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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/528,477	03/18/2005	Christopher Luckhurst	06275-448US1	8642

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EXAMINER	
O'DELL, DAVID K	
ART UNIT	PAPER NUMBER
1625	
MAIL DATE	DELIVERY MODE
08/26/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/528,477	LUCKHURST ET AL.	
	Examiner	Art Unit	
	David K. O'Dell	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-9 and 12-14* is/are pending in the application.

4a) Of the above claim(s) *12-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 4-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/12/2008, 8/1/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

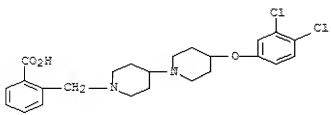
1. This application is a 371 of PCT/SE03/01425 filed 09/12/2003 and claims priority to Swedish application 0202838-9 filed 09/24/2002.

Claims 1-2, 4-9, 12-14 are pending.

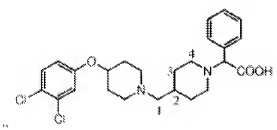
Response to Arguments and Remarks

3. Applicant's arguments filed on August 1, 2008 have been fully considered but they are not fully persuasive. The rejections of the claims under 35 U.S.C. 103 (a), is maintained. Apparently the examiner had misinterpreted the species election as being drawn to the following compound:

RN 367495-44-1 CAPLUS
CN Benzoic acid, 2-[[4-(3,4-dichlorophenoxy)[1,4'-bipiperidin]-1'-yl]methyl]-
(CA INDEX NAME)



however as correctly pointed out by the applicant the compound actually elected was:



The closeness in nomenclature and the failure of the applicant to provide drawings no doubt led to such confusion. While this does in fact impact the 103(a) rejection of the elected species, the rejection is still valid because the compound that was the basis of the rejection is another species of the specification that is claimed. The rejection of the remaining claims under 103 (a) is maintained for the reasons of record (although the rejection of claim 6 is withdrawn). While ordinarily the insertion of a methylene group is not an obvious change, clearly this is taught by Ko et. al. and is well known in this very narrow field. All of these compounds have the same utility. The applicant' representative has suggested that since Ko's compounds differ in the linkage of the piperidines from that of Lawrence (3,1 vs. 4,1 repsectively.), it would not occur to one of ordinary skill that a methylene linkage could be inserted in the 4,1 compounds. The examiner disagrees. It is the teaching of the prior art as a whole that suggests this change, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). It weighs heavily that both the compounds of Lawrence, Ko and the instant case have exactly the same utility and that the instantly claimed compounds differ from that of Lawrence by a change taught by Ko. It is remarkable that the applicant's representative is suggesting that the position of the attachment of the piperidine would bring about "significant changes (either beneficial or deleterious) in biological activity of the claimed compounds because their biological activity is highly dependent on their capability of being able to "fit" to specific chemokine receptors." (Remarks at pg. 5), given that the instant claims are invariably drawn to ambiguous points of attachment for numerous substituents. Y for instance is any "heterocyclylene" attached in any way to the R2

bearing carbon and also attached in any way to the group Z. Moreover all the "aryl" and "heterocyclyl" moieties "unless otherwise stated" are optionally substituted by various groups in ambiguous positions that are themselves linked in an ambiguous matter. In addition the latter are furhter ambiguously attached and further ambiguously optionally substituted by other groups which are independently ambiguously optionally susbtituted with other groups which form ambiguously attached rings. The admission by the applicant's representative may form the basis of an enablement rejection.

The applicant has argued essentially the same line of reasoning in traversing the double patenting rejections over 6,903,115 and 7,179,922. The examiner agrees that the rejection over 10/556,107 cannot be maintained since the change of phenyl for benzyl has not been taught on the nitrogen of the piperidine and withdraws this rejection. The rejection over 10/508,331 is maintained for the reasons of record since position isomers are in fact *prima facie* obvious. The teaching of Lawrence could be used to substantiate this finding, but is not necessary. It is routine for a chemist to make position isomers.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

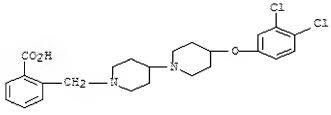
3. Claims 1-2, 4, 5, 7-9, are rejected under 35 U.S.C. 103(a) as being unpatentable over Lawrence, et. al. WO 2001077101 A1 (cited on the IDS) in view of Ko et. al. WO 200035877 (cited on the IDS). The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

Determination of the scope and content of the prior art

(MPEP 2141.01)

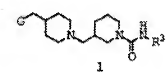
Lawrence, et. al. teaches compounds that are analogs of the compounds of the instant case that have the same utility. Lawrence teaches hundreds of compounds including many compounds with an N–benzyl moiety or an (CH2)-heteroaryl moiety on the piperidine compound, including the following compound:

RN 367455-44-1 CAPLUS
CN Benzoic acid, 2-[[4-(3,4-dichlorophenoxy)[1,4'-bipiperidin]-1'-yl]methyl]-
(CA INDEX NAME)

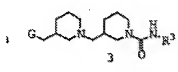


Ko et. al. teaches the presence of a methylene group between the two piperidine rings is also a core pharmacophore of CCR5 activity. A thousand or more compounds bearing a methylene linkage between the two piperidines in Table 1, were prepared.

Table 1*



1



3

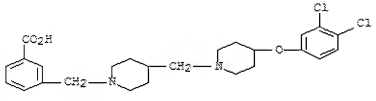
pg. 138

Ascertainment of the difference between the prior art and the claims

It is clear that the prior art differs from the instantly claimed compounds by the presence of a methylene group between the piperidine rings in the later.

A species of the instant claims specifically delineated in the specification is shown below, where Y is phenyl, Z is CO2H, R1 and R2 are H, where X is O and R1 is phenyl

RN 676518-36-8 CAPLUS
CN Benzoic acid, 3-[[4-[[4-(3,4-dichlorophenoxy)-1-piperidinyl]methyl]-1-piperidinyl]methyl]- (CA INDEX NAME)



The only difference is a methylene group. Other such species to species comparisons could also be drawn.

Finding of prima facie obviousness

Rational and Motivation

(MPEP 2142-2143)

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use analogs of those of Lawrence et. al. to produce the instant invention. Analogs differing only in the length of an alkyl chain , are *prima facie* obvious, and require no secondary teaching, however Ko et. al. teaches this modification. The experienced Ph.D. synthetic organic chemist, who would make Applicants' compounds, would be motivated to prepare these compounds on the expectation that such close analogues would have similar properties and upon the routine nature of such experimentation in the art of medicinal chemistry. It would be routine for the chemist to insert a methylene at the point of attachment in order to increase potency and to establish better patent protection for his/her compounds. See *In re Coes, Jr.* (CCPA 1949) 173 F2d 1012, 81 USPQ 369.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of

the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

One of ordinary skill is also one of "ordinary creativity, not an automaton". See Leapfrog Enterprises Inc. v. Fisher-Price. and Mattel Inc. UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT "An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See KSR Int'l Co. v. Teleflex Inc., 550 U.S. , 2007 U.S. LEXIS 4745, 2007 WL 1237837, at 12 (2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 1-2, 4-9, are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1,2, 4-7, 9-11 of copending

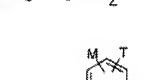
Application No. 10/508,331. Although the conflicting claims are not identical, they are not patentably distinct from each other because the '331 application is drawn to position isomers of the elected species (and the generic claims as well). In claim 1 of the '331 application:

A compound of formula (I):

(I)

wherein:

Z is



X is O,

Y is CH_2;

R^1 is aryl

It is clear that the instant case is drawn to 4-piperidinyl compounds, while the '331 application is drawn towards 3-piperidinyl compounds. Positional isomers, having the same radical on different positions of the molecule, are *prima facie* obvious, and require no secondary teaching. The experienced Ph.D. synthetic organic chemist, who would make Applicants' compounds, would be motivated to prepare these position isomers based on the expectation that such close analogues would have similar properties and upon the routine nature of such position isomer experimentation in the art of medicinal chemistry. It would be routine for the chemist to vary the point of attachment in order to increase potency and to establish better patent protection for her compounds. *In re JONES* 74 USPQ 152 (4-methyl naphthyl-1-acetic acid and 2-methyl

naphthyl-1-acetic acid obvious over a reference teaching 1-methyl naphthyl-2-acetic acid), quoted with approval by *Ex parte MOWRY AND SEYMOUR* 91 USPQ 219, *Ex parte Ullyot* 103 USPQ 185 (4-hydroxy-1-oxo-1,2,3,4-tetrahydroisoquinoline obvious over a reference teaching 4-hydroxy-2-oxo-1,2,3,4-tetrahydroquinoline), "[p]osition isomers are recognized by chemists as similar materials", *Ex parte BIEL* 124 USPQ 109 (N-ethyl-3-piperidyl diphenylacetate obvious over a reference teaching N-alkyl-4-piperidyl diphenylacetate), "[appellant's arguments] do not, in any way, obviate the plain fact that appellant's DACTIL is an isomer of McElvain et al.'s compound. This close relationship places a burden on appellant to show some unobvious or unexpected beneficial properties in his compound in order to establish patentability", *Ex parte Henkel* 130 USPQ 474, (1-phenyl-3-methyl-4-hydroxypyrazole obvious over reference teaching 3-phenyl-5-methyl-4-hydroxypyrazole), "appellants have made no comparative showing here establishing the distinguishing characteristics they allege which we might consider as evidence that the claimed compounds are unobvious. It is clear from *In re Henze*, supra, and the authorities it cites, that at least this much is necessary to establish patentability in adjacent homologs and **position isomers** (emphasis added)".

In re Surrey 138 USPQ 67, (2,6-dimethylphenyl-N-(3-dimethylaminopropyl) carbamate obvious over a reference teaching 2,4-dimethylphenyl N-(3-dimethylaminopropyl) carbamate), *In re MEHTA* 146 USPQ 284, (2-(1-methyl)-pyrrolidylmethyl benzilate obvious over a reference teaching 3-(1-methyl)-pyrrolidylmethyl benzilate), "[t]he fact that a **position isomer** (emphasis added) of a compound is known is some evidence of the obviousness of that compound. **Position isomerism** (emphasis added) is a fact of close *structural* (emphasis in original) similarity ...".*Deutsche Gold-Und Silber-Scheideanstalt Vormals Roessler v. Commissioner of*

Patents, 148 USPQ 412, (1-azaphenothiazines obvious over references teaching 2-azaphenothiazines, 3-azaphenothiazines, and 4-azaphenothiazines), *In re Crounse*, 150 USPQ 554 (dye with *para* ($CONH_2$) and *ortho* (OCH_3) obvious over a dye with the same nucleus and *meta* ($CONH_2$) and *para* (OCH_3) group), *Ex parte Allais*, 152 USPQ 66, (3-β-aminopropyl-6-methoxyindole obvious over a reference teaching 3-β-aminopropyl-5-methoxyindole), *In re Wiechert* 152 USPQ 247, (1-methyl dihydrotestosterones obvious over a reference teaching 2-methyl dihydrotestosterones), *Monsanto Company v. Rohm and Haas Company*, 164 USPQ 556, at 559, (3',4'-dichloropropionanilide obvious over references teaching 2',4'-dichloropropionanilide and 2',5'-dichloropropionanilide), *Ex parte Naito and Nakagawa*, 168 USPQ 437, (3-phenyl-5-alkyl-isothiazole-4-carboxylic acid obvious over a reference teaching 5-phenyl-3-alkyl-isothiazole-4-carboxylic acid), "[t]his merely involves **position isomers** (emphasis added) and under the decisions cited, the examiner's holding of *prima facie* obviousness is warranted." *In re Fouche*, 169 USPQ 429, (10-aliphatic substituted derivatives of dibenzo[a,d]cycloheptadiene obvious over reference teaching 5-aliphatic substituted derivatives of dibenzo[a,d]cycloheptadiene). *In re Hass* 60 USPQ 552, which found a *prima facia* case of obviousness of 1-chloro-1-nitrobutane over 1-chloro-1-nitroisobutane taught in the prior art, *Ex parte Ullyot*, 103 USPQ 185, which found a *prima facia* case of of 2-oxo-quinolines obvious over prior art a 1-oxo-isoquinoline, *In re FINLEY,* 81 USPQ 383, 2-ethyl hexyl salicylate over octyl salicylate.

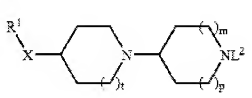
Ex parte Engelhardt, 208 USPQ 343 at 349, "[i]f functional groups capable of withdrawing or repelling electrons are located in the chain or **ring** (emphasis added) of a biologically active compound, transfer of such groups to other positions in which their electronic

effects are lessened or enhanced may alter the biological activity of the modified compound. Hence, **position isomerism** (emphasis added) has been used as a tool to obtain new and useful drugs", *In re Grabiak* 226 USPQ 870, "[w]hen chemical compounds have "very close" structural similarities and similar utilities, without more a *prima facie* case may be made", *In re Deuel* 34 USPQ2d 1210, "a known compound may suggest its analogs or isomers, either geometric isomers (*cis* v. *trans*) or **position isomers** (emphasis added) (*e.g. ortho v. para*)".

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

5. Claims 1-2, 4-9 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 9-18 of U.S. patent 7,179,922. Although the conflicting claims are not identical, they are not patentably distinct from each other because the '922 patent is drawn to analogs of the generic claims. In claim 1 of the '922 patent:

1. A compound of formula (XIIIa):



(XIIIa)

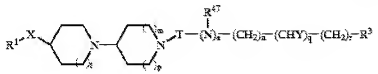
wherein:
L^2 is benzyl;
t is 1;
m and p are 1;
X is O;
R^1 is phenyl optionally substituted with one or more of halogen,

It is clear that the only difference here is the presence of a methylene group in the instant case. See the 103 (a) rejection above for the obviousness of this modification in the CCR5 receptor art.

6. Claims 1-2, 4-9 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-8, 10-13 of U.S. patent 6,903,115. Although the conflicting claims are not identical, they are not patentably distinct from each other because the '922 patent is drawn to analogs of the generic claims (when Y of the instant case is "heterocyclylene"). In claim 1 of the '922 application:

1. A compound of formula (I):

(I)



wherein:

I. q and s are, 0

II. n and r are, 0,

III. t, m and p are 1;

IV. X is O;

VI. T is CH_2;

VII. R^1 is phenyl optionally substituted by halogen,

VIII. 1 R^{47} hydrogen,

IX. R^3 is heterocycyl,

1 R^3 are optionally substituted

It is clear that the only difference here is the presence of a methylene group in the instant case. See the 103 (a) rejection above for the obviousness of this modification in the CCR5 receptor art.

Conclusion

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone number is (571)272-9071. The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571)272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

D.K.O.

/Rita J. Desai/
Primary Examiner, Art Unit 1625